



Management of Pulmonary Arterial Hypertension

Jennalyn D. Mayeux¹ · Irene Z. Pan² · John Dechand² · Joshua A. Jacobs² · Tara L. Jones³ · Stephen H. McKellar⁴ · Emily Beck¹ · Nathan D. Hatton¹ · John J. Ryan³

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Abstract

Purpose of Review This review focuses on the therapeutic management and individualized approach to Group 1 pulmonary arterial hypertension (PAH), utilizing Food and Drug Administration-approved PAH-specific therapies and various interventional and surgical options for PAH.

Recent Findings The paradigm for the optimal management of PAH has shifted in recent years. Upfront combination therapy with an endothelin receptor antagonist and a phosphodiesterase 5 inhibitor is now widely accepted as standard of care. In addition, there is increasing emphasis on starting prostanoids early in order to delay time to clinical worsening. However, less is known regarding which prostanoid agent to initiate and the optimum time to do so. In order to facilitate shared decision-making, there is an increasing need for decision tools based on guidelines and collective clinical experiences to navigate between pharmacologic and interventional treatments, as well as explore innovative, therapeutic pathways for PAH.

Summary The management of PAH has become increasingly complex. With a growing number of PAH-specific therapies, intimate knowledge of the therapeutics and the potential barriers to adherence are integral to providing optimal care for this high-risk patient population. While current PAH-specific therapies largely mediate their effects through pulmonary vasodilation, ongoing research efforts are focused on ways to disrupt the mechanisms leading to pulmonary vascular remodeling. By targeting aberrations identified in the metabolism and proliferative state of pulmonary vascular cells, novel PAH treatment pathways may be just on the horizon.

Keywords Pulmonary hypertension · Therapeutics · Right heart failure · Pharmacology · Prostaglandin · Prostacyclin

Introduction

Pulmonary hypertension (PH) describes an abnormal elevation in pulmonary arterial blood pressure [1]. The World

Health Organization (WHO) classifies PH into five groups based on shared histology and pathophysiology. Group 1 pulmonary arterial hypertension (PAH) is a rare form of PH characterized by plexogenic vascular remodeling. Causes for Group 1 PAH include idiopathic and familial PH, as well as PH associated with conditions such as collagen vascular disease, congenital shunts, cirrhosis and portal hypertension, human immunodeficiency virus (HIV), hemoglobinopathies, and schistosomiasis. Group 1 PAH also includes PH associated with drugs, such as anorexigens or amphetamines. Group 2 PH is the collection of PH syndromes resulting from left ventricular (LV) or left-sided valvular disease, such as heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), or valvular heart disease. Group 3 PH is PH secondary to chronic lung diseases, hypoxia, or both. This group of PH is typically characterized by mild elevations in pulmonary artery pressure (PAP), relative to patients with other types of PH. Group 4 PH is due to pulmonary arterial obstruction and commonly known as chronic thromboembolic pulmonary hypertension (CTEPH).

Jennalyn D. Mayeux and Irene Z. Pan contributed equally to this work.

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✉ John J. Ryan
john.ryan@hsc.utah.edu

¹ Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Utah, Salt Lake City, UT 84132, USA

² Department of Pharmacy, University of Utah Health, Salt Lake City, UT 84132, USA

³ Division of Cardiovascular Medicine, Department of Medicine, University of Utah, 30 North 1900 East, Room 4A100, Salt Lake City, UT 84132, USA

⁴ Division of Cardiothoracic Surgery, Department of Surgery, University of Utah, Salt Lake City, UT 84132, USA

This category of PH is particularly unique as it represents a curable form of PH that does not require lung transplantation. Group 5 PH represents a heterogeneous collection of PH syndromes secondary to systemic diseases (e.g., sarcoidosis, histiocytosis X), hematological disorders (e.g., polycythemia vera, chronic myeloid leukemia), and extrinsic compression of the pulmonary artery. This classification system has practical significance as contemporary PAH treatments have increasingly demonstrated inconsistent benefit and even potential signals of harm across other types of PH [2].

The focus of this review is the therapeutic management of Group 1 PAH. The review will discuss approved and emerging treatment pathways, Food and Drug Administration (FDA)-approved PAH-specific therapies, and personalization of PAH care, in addition to interventional and surgical options for PAH.

Currently Approved Treatment Pathways

The pathogenesis of PAH is diverse and very complex. As more clinical trial and registry data becomes available, our understanding of the development and progression of this rare disease continues to evolve. Multiple mechanisms occur at the cellular and tissue level that potentiate smooth muscle cell proliferation, endothelial cell dysfunction, inflammation, and remodeling of the pulmonary vasculature. Together, these physiological alterations result in pathologic transformations leading to excessive vasoconstriction, medial hypertrophy, intimal fibrosis, and formation of plexiform lesions [3, 4]. Contemporary PAH therapies target one of three major pathways implicated in disease progression: nitric oxide (NO), endothelin-1 (ET-1), and prostacyclin (PGI₂) pathways. In a small minority of patients with PAH, excessive vasoconstriction plays a predominant role in increasing pulmonary vascular resistance (PVR)—mediated in large part by an influx of calcium via long-lasting calcium channels in vascular smooth muscle cells [5]. Targeting one or more of these pathways has become the current standard of practice for the medical management of PAH [6]. Therapies are available orally (Table 1) and in parenteral and inhaled forms (Table 2). Clinical trials have shown that these therapies play an important role in improving quality of life, and some have even shown a reduction in mortality rates in PAH (Table 3). However, PAH remains a high mortality disease with no cure.

Nitric Oxide Pathway

In PAH, NO production is chronically impaired. NO is an endothelium-derived vasoactive mediator that increases the production of cyclic guanosine monophosphate (cGMP) through the activation of soluble guanylate cyclase (sGC). In doing so, NO acts to stimulate vasodilation and inhibit proliferation within vascular smooth muscle cells [3, 4]. Currently,

there are two drug classes targeting this pathway, phosphodiesterase type-5 inhibitors (PDE5i) and sGC stimulators. Phosphodiesterase type-5 (PDE5) is an enzyme found in high concentrations within the pulmonary vasculature that works to catalyze the conversion of cGMP to guanosine monophosphate (GMP). Inhibitors of the PDE-5 enzyme, such as sildenafil and tadalafil, enhance the NO-dependent, cGMP-mediated pathway by preventing the breakdown of cGMP, while riociguat, an sGC stimulator, works directly to increase the production of cGMP, resulting in vasodilation and antiproliferative effects [57].

Endothelin Pathway

Endothelin-1 is a potent vasoconstrictor and key driver of pulmonary vascular remodeling through its actions on endothelin receptor A (ET_A) and endothelin receptor B (ET_B) [3]. Endothelin-1 is upregulated in the vascular endothelial cells of patients with pulmonary hypertension. By binding to ET_A and ET_B receptors located in smooth muscle cells, ET-1 stimulates cellular proliferation, fibrosis, inflammation, and vasoconstriction [4, 58]. The effects of ET-1 via ET_B on endothelial cells result in increased production of prostacyclin and NO and subsequent vasodilation [3, 59]. Both ET_A and ET_B receptors are found in high concentrations within the pulmonary vasculature, and as such, serve as an important focus for targeted drug therapy [59]. There are currently three FDA-approved endothelin-receptor antagonists (ERA) with varying degrees of affinity for ET_A and ET_B receptors: ambrisentan, bosentan, and macitentan.

Prostacyclin Pathway

The final pathway involves prostacyclin, a potent vasodilator produced predominantly in the vascular endothelium. The vasodilatory effects of prostacyclin, also referred to as PGI₂, result from PGI₂ stimulation of the prostaglandin I₂ (IP) receptor, leading to increased generation of cyclic adenosine monophosphate (cAMP). Additionally, PGI₂ inhibits platelet aggregation and possesses antiproliferative properties [3, 60]. However, in PAH, PGI₂ synthesis is suppressed, whereas levels of thromboxane A₂, an endogenous vasoconstrictor and platelet agonist, are increased [61]. Drug therapies targeting this imbalance within the pulmonary arteries include PGI₂ analogs, such as epoprostenol, treprostinil, and iloprost, and PGI₂ receptor agonists, such as selexipag [62].

Calcium Channel Blockers

Calcium channel blockers (CCB) are indicated in patients with a positive acute vasoreactivity test. Common CCBs used for

Table 1 Oral PAH-Specific Therapies

Medication	Target dose	Adverse effects	REMS requirement	PH group WHO-FC	Notable clinical trials
Calcium channel blockers					
Amlodipine [7]	20 mg daily	Peripheral edema, hypotension, dizziness, GI distress	No	Group 1 WHO-FC II-III	Sitbon 2005 [8]
Nifedipine [9]	120 to 240 mg daily		No		Rich et al. 1992 [10] Sitbon 2005 [8]
Diltiazem [11]	240 to 720 mg daily	Peripheral edema, hypotension, bradycardia, cardiac conduction delay, GI distress	No		Rich et al. 1992 [10] Sitbon 2005 [8]
PDE-5 inhibitors					
Sildenafil [12]	20 mg three times daily	Headache, flushing, hypotension, dyspepsia, nausea, myalgias, epistaxis, visual disturbances, insomnia	No	Group 1 WHO-FC II-IV	SUPER 2005 [13] SERAPH 2005 [14] Singh 2006 [15] PACES 2008 [16] Vizza 2017 [17] PHIRST 2009 [19] AMBITION 2015 [20]
Tadalafil [18]	40 mg daily		No	Group 1 WHO-FC II-IV	
Endothelin receptor antagonists					
Ambrisentan [21]	10 mg daily	Peripheral edema, flushing, headache, dyspepsia, anemia, nasal congestion, bronchitis, sinusitis	Yes	Group 1 WHO-FC II-IV	ARIES-1 2008 [22] ARIES-2 2008 [22] AMBITION 2015 [20]
Bosentan [23]	< 40 kg: 62.5 mg twice daily ≥ 40 kg: 125 mg twice daily	Peripheral edema, headache, increased serum ALT and AST, respiratory tract infection, hypotension, flushing, sinusitis, anemia, hepatotoxicity (rare)	Yes	Group 1 WHO-FC II-IV	Chamick et al. 2001 [24] BREATHE-1 2002 [25] BREATHE-2 2004 [26] BREATHE-5 2006 [27] EARLY 2008 [28] COMPASS-2 2015 [29] SERAPHIN 2013 [31] MERIT-1 2017 [32]
Macitentan [30]	10 mg daily	Headache, anemia, nasopharyngitis, pharyngitis, bronchitis, UTIs, anemia	Yes	Groups 1 and 4 WHO-FC II-IV	
Soluble guanylate cyclase stimulator					
Riociguat [33]	2.5 mg three times daily	Headache, dyspepsia, dizziness, hypotension, anemia, GI distress, hemoptysis (rare)	Yes	Groups 1 and 4 WHO-FC II-IV	PATENT-1 2013 [34] CHEST-1 2013 [35] PATENT PLUS 2015 [36]
Prostacyclin agonist					
Selexipag [37]	Maximum dose tolerated up to 1600 mcg twice daily	Headache, flushing, diarrhea, nausea, flushing, flu-like symptoms, myalgia, jaw pain, skin rash	No	Group 1 WHO-FC II-III	GRIPHON 2015 [38] TRITON 2020
Prostacyclin analogue					
Treprostinil, oral [39]	Max dose determined by tolerability	Flushing, headache, diarrhea, nausea, vomiting, abdominal pain, limb/jaw pain, hypokalemia	No	Group 1 WHO-FC II-III	FREEDOM-C 2012 [40] FREEDOM-C2 2013 [41] FREEDOM-M 2013 [42] FREEDOM-EV 2020 [43]

ALT, alanine transaminase; AST, aspartate transaminase; GI, gastrointestinal; PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase 5; PH, pulmonary hypertension; REMS, risk evaluation and mitigation strategy; UTI, urinary tract infection; WHO-FC, World Health Organization Functional Class

Table 2 Parenteral and inhaled PAH-specific therapies

Medication	Target dose	Adverse effects	REMS requirement	PH group WHO-FC	Notable clinical trials
Prostacyclin analogues					
Epoprostenol* [44]	25–40 ng/kg/min or higher based on clinical response and tolerability	Headache, flushing, tachycardia, hypotension, chest pain, dizziness, GI distress, flu-like symptoms, anxiety, skin rash, myalgia, arthralgia, jaw pain	No	Group 1 WHO-FC III-IV	Rubin et al. 1990 [45] Barst et al. 1996 [46] Badesch 2000 [47]
Treprostinil IV/SQ* [48] Inhaled [49]	40–80 ng/kg/min or higher based on clinical response and tolerability 54 meg (9 inhalations) four times daily	Flushing, vasodilation, headache, GI distress, infusion site reaction and/or pain, jaw pain, edema, hypotension, cough and throat irritation (inhaled)	No	Group 1 WHO-FC II-III	Simonneau et al. 2002 [50] TRUST 2010 [51] TRIUMPH I 2010 [52]
Iloprost [53]	5 meg nine times daily	Flushing, headache, hypotension, trismus, nausea, jaw pain, flu-like symptoms, cough, insomnia	No	Group 1 WHO-FC III-IV	AIR 2002 [54] STEP 2006 [55] COMBI 2006 [56]

*Maximum or optimal dose has not been well-defined in the literature. There is substantial variability in maximally tolerated doses achieved between patients [48]

GI, gastrointestinal; IV, intravenous; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; REMS, risk evaluation and mitigation strategy; SQ, subcutaneous; WHO-FC, World Health Organization Functional Class

PAH include nifedipine, amlodipine, and diltiazem. Diltiazem is typically reserved for patients with tachycardia or other comorbidities requiring rate control and avoided in patients with worsening right ventricular failure or bradycardia. Effective doses are higher than what is typically seen for other indications (Table 1). Patients should be started on a low dose and gradually titrated up as tolerated [57]. Common adverse drug reactions include peripheral edema, systemic hypotension, nausea, gastrointestinal distress, and bradycardia, in the setting of diltiazem [7, 9, 11]. Monotherapy with a CCB is indicated only in patients who achieve the desired dose, establish improved hemodynamics after 3–4 months of therapy, and maintain WHO Functional Class (FC) I-II status. In patients who cannot tolerate therapy or experience worsening hemodynamics or functionality, alternative PAH-specific therapy is recommended [57].

Calcium channel blockers were initially studied in the acute setting in patients who were given nifedipine 20 mg or diltiazem 60 mg hourly. Of the patients who responded to CCB therapy, the mean reduction in PVR and PAP were 60% and 48%, respectively [63]. A subsequent study demonstrated improved 5-year survival in patients who responded to CCBs compared to those who did not (94% vs. 55%; $p = 0.003$) [10]. However, less than 10% of PAH patients were found to be long-term responders to CCB therapy [8, 10, 64].

Phosphodiesterase Type-5 Inhibitors

For over a decade, PDE5is have remained the most widely prescribed class of PAH-specific therapies. These agents are arguably the easiest to initiate due to relative ease of procurement and generic availability. As such, these agents are typically the initial therapy prescribed for patients diagnosed with PAH.

Although initially approved in 1998 for use in erectile dysfunction [65], the role of sildenafil soon expanded due to its actions on PDE5 receptors within the pulmonary vasculature, and sildenafil was approved by the FDA for the treatment of PAH in 2005 [12]. Early sildenafil trials, the vast majority of which included ≤ 30 patients, tested doses up to 100 mg three times daily [66]. In these studies, sildenafil demonstrated efficacy in a number of clinical outcomes with incremental benefit at higher sildenafil doses. The 2005 SUPER trial, a randomized, placebo-controlled trial, demonstrated improvements in WHO-FC, reduction in mean PAP, and reduction in PVR that incrementally improved with higher doses [13]. No significant difference was found between sildenafil 20 mg, 40 mg, and 80 mg three times daily in WHO-FC II-III, treatment-naïve patients with respect to the primary outcome of 6-min walk distance (6MWD) [13]. Moreover, sildenafil has also been shown to improve outcomes even when added to advanced therapies such as intravenous (IV) epoprostenol.

Table 3 Notable Clinical Trials of PAH-Specific Therapies

Clinical trials	N	Duration (week)	Background PAH-specific therapy	Comparator group(s)	Primary endpoint	Results (S or NS)	PMID
Oral PAH-specific therapies							
Calcium channel blockers							
Rich et al. 1987	13	13–20 months	No	N/A	N/A	Sustained reductions in mPAP and PVR in CCB responders (N/A)	2954725
Rich et al. 1992	64	4 months–5 years	No	CCB non-responders	All-cause mortality	26% deemed CCB responders. Improved survival in CCB responders compared to non-responders (S)	1603139
Sitbon et al. 2005	70	5.3 ± 3.8 years	No	N/A	Characterize and define proportion of long-term CCB responders in IPAH	6.8% deemed long-term CCB responders (54% of acute responders continued to show improvement a 1 year on CCB therapy) (N/A)	15939821
Sildenafil							
SUPER 2005	277	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW not improved (NS)	16291984
SERAPH 2005	26	16	No	Bosentan	Δ RV mass	Significant reduction in RV mass (S), 6MWD improved (S)	15750042
Singh et al. 2006	20	6	No	Placebo	Δ 6MWD	6MWD improved (S)	16569546
Badesch et al. 2007	84	12	No	Placebo	Δ 6MWD	6MWD improved (S)	17985403
PACES 2008	267	16	Epoprostenol	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	18936500
Vizza et al. 2017	103	12	Bosentan	Placebo	Δ 6MWD	6MWD not improved (NS)	28874133
Tadalafil							
PHIRST 2009	405	16	No, or bosentan (54%)	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	19470885
AMBITION 2015	500	78	No (but 1 of the 3 study arms was upfront combination therapy with tadalafil and ambrisentan)	Ambrisentan monotherapy or Tadalafil monotherapy	TTCF (including death)	TTCF improved (S), 6MWD improved (S)	26308684
Ambrisentan							
ARIES-1 2008	202	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW not improved (NS)	18506008
ARIES-2 2008	192	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	18506008
AMBITION 2015	500	78	No (but 1 of the 3 study arms was upfront combination therapy with tadalafil and ambrisentan)	Ambrisentan monotherapy or Tadalafil monotherapy	TTCF (including death)	TTCF improved (S), 6MWD improved (S)	26308684

Table 3 (continued)

Clinical trials	N	Duration (week)	Background PAH-specific therapy	Comparator group(s)	Primary endpoint	Results (S or NS)	PMID
Bosentan							
Channick et al. 2001	32	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	11597664
BREATHE-1 2002	213	16	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	11907289
BREATHE-2 2004	33	16	Epoprostenol	Placebo	Δ PVR	PVR not improved (NS), 6MWD not improved (NS)	15358690
BREATHE-5 2006	54	16	No	Placebo	SaO ₂ , PVR	6MWD not improved (NS), SaO ₂ not reduced, PVR improved (S)	16801459
EARLY 2008	185	24	No, or sildenafil (16%)	Placebo	Δ PVR and Δ 6MWD	6MWD improved (S), PVR improved (S)	18572079
COMPASS-2 2015	334	16	Sildenafil	Placebo	TTCW (including death)	6MWD not improved (NS), TTCW not improved (NS), 6MWD improved (S)	26113687
Macitentan							
SERAPHIN 2013	742	115	No, or PDE5i (61%), or oral (5%) or inhaled prostanoid	Placebo	TTCW (including death)	TTCW improved (S)	23984728
MERIT-1 2017	80	16	No, or PDE5i only (46%), or PDE5i + oral or inhaled prostanoid (13%), or oral or inhaled prostanoid alone (3%)	Placebo	Δ PVR	PVR improved (S), 6MWD improved (S)	28919201
Riociguat							
PATENT-1 2013	443	12	No, or ERA (44% - mostly bosentan), or prostanoid (6% - mostly inhaled iloprost)	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S), PVR improved (S)	23883378
CHEST-1 2013	261	16	No	Placebo	Δ 6MWD	6MWD improved (S), PVR improved (S)	23883377
PATENT PLUS 2015	18	12	Sildenafil	Placebo	Δ Supine SBP	Terminated due to excess SAE in the treatment group and no clear benefit	25657022
RESPITE 2017	61	24	ERA	None	Δ 6MWD, Δ NT-proBNP, Δ WHO-FC, Δ hemodynamics	6MWD improved (S), NT-proBN WHO-FC improved (S), hemody	
REPLACE 2020	226	24	ERA	PDE5i	Clinical improvement	Clinical improvement (S)	
Selexipag							
GRIPHON 2015	1156	71	No, or ERA (15%), PDE5i (32%), or both (33%)	Placebo	TTCW (including death)	TTCW improved (S)	26699168
TRITON 2020	247	26	Macitentan and tadalafil	Placebo	Δ PVR	PVR not improved (NS), 6MWD not improved (NS), TTCW not improved (NS)	NCT02558231

Table 3 (continued)

Clinical trials	N	Duration (week)	Background PAH-specific therapy	Comparator group(s)	Primary endpoint	Results (S or NS)	PMID
Oral treprostinil							
FREEDOM-C 2012	350	16	ERA and/or PDE-5i	Placebo	Δ 6MWD	6MWD not improved (NS), TTCW not improved (NS)	22628490
FREEDOM-C2 2013	310	16	ERA and/or PDE-5i	Placebo	Δ 6MWD	6MWD not improved (NS), TTCW not improved (NS)	23669822
FREEDOM-M 2013	349	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW not improved (NS)	23307827
FREEDOM-EV 2020	690	22	ERA alone (28%), or PDE-5i or SGC stimulator alone (72%)	Placebo	TTCW	TTCW improved (S), 6MWD not improved (NS)	31765604
Parenteral and inhaled PAH-specific therapies							
Epoprostenol							
Rubin et al. 1990	23	8	No	Conventional therapy*	Δ 6MWD and Δ pulmonary hemodynamics	6MWD improved (NS), pulmonary hemodynamics improved (NS)	2107780
Barst et al. 1996	81	12	No	Conventional therapy*	Δ 6MWD	6MWD improved (S), PVR and mPAP improved (S), survival improved (S)	8532025
Badesch et al. 2000	111	12	No	Conventional therapy*	Δ 6MWD	6MWD improved (S), PVR and mPAP improved (S)	10733441
Treprostinil							
Simonneau et al. 2002	470	12	No	Placebo	Δ 6MWD	6MWD improved (S), PVR and mPAP improved (S)	11897647
TRUST 2010	44	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved in post-hoc analysis (S)	20022264
TRIUMPH I 2010	235	12	Bosentan (70%) or sildenafil (30%)	Placebo	Δ 6MWD	6MWD improved (S), TTCW not improved (NS)	20430262
Iloprost							
AIR 2002	203	12	No	Placebo	Δ 6MWD and Δ WHO-FC	6MWD & WHO-FC improved (S), PVR improved (S), TTCW not improved (NS)	12151469
STEP 2006	67	12	Bosentan	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	16946127
COMBI 2006	40	12	Bosentan	Bosentan monotherapy	Δ 6MWD	Terminated for futility, 6MWD not improved (NS)	17012628

*Could include: CCB, warfarin, supplemental oxygen, digoxin, and/or diuretics, as deemed appropriate

6MWD, 6-min walk distance; CCB, calcium channel blocker; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; N/A, not applicable; NS, not statistically significant; PVR, pulmonary vascular resistance; S, statistically significant; SAE, serious adverse effect; SaO₂, systemic arterial blood oxygen saturation; TTCF, time to clinical failure; TTCW, time to clinical worsening

The 2008 PACES trial randomized patients on IV epoprostenol to sildenafil 80 mg three times daily or placebo [16]. The addition of sildenafil at 80 mg three times daily to an IV prostanoid improved 6MWD in comparison to the placebo arm. This further solidified its place in therapy and added to the data supporting combination therapy. Although there has been some interest over the years regarding use of higher sildenafil doses such as 40 mg or even 80 mg three times daily, the large sample size data available do not support this strategy. Based on data from the SUPER trial, it has been hypothesized that adequate inhibition of PDE5 is achieved with 20 mg dosed three times daily [13]. Thus, 20 mg three times daily became the FDA-approved dose for PAH [12]. Notwithstanding the evidence for higher doses, obtaining insurance approval for doses higher than the FDA-approved dose of 20 mg three times daily is very difficult.

The other widely available agent in this class, tadalafil, received FDA-approval in 2009. Tadalafil is more convenient than its predecessor given its longer half-life and once daily dosing [18]. Unlike the mixed data with sildenafil dosing, the PHIRST trial demonstrated tadalafil 40 mg once daily was indisputably the target dose [19]. Tadalafil 40 mg daily demonstrated improvements in 6MWD and time to clinical worsening (TTCW) in a mixture of treatment-naïve patients and patients on background therapy with bosentan. Both PDE5is carry similar adverse effect profiles, the most common being headache, flushing, myalgia, and dyspepsia. These adverse effects rarely result in the need for discontinuation and typically resolve over time.

Soluble Guanylate Cyclase Stimulators

As a member of the newest class of PAH-specific therapies, riociguat, a sGC stimulator, has established its role among the armamentarium of agents that target the NO pathway. In addition to its role in Group 1 PAH, riociguat is currently the only PAH-specific therapy that also carries FDA approval for Group 4 PH, or inoperable or persistent CTEPH [6, 57]. In the PATENT-1 and CHEST-1 trials, riociguat 2.5 mg three times daily significantly improved the primary outcome of 6MWD by 30 m and 39 m, in PAH and CTEPH, respectively [34, 35]. In PATENT-1, this effect was seen in both treatment-naïve patients, as well as patients on background therapy with an ERA. The secondary endpoints of reduction in PVR and N-terminal probrain natriuretic peptide (NT-proBNP) and improvement in WHO-FC were consistent between both trials. Though only PATENT-1 showed an improvement in TTCW, this endpoint should be interpreted with caution due to the small overall number of events (8 vs. 3) [6]. In addition, the RESPITE trial demonstrated a potential benefit in transitioning from PDE5i therapy to riociguat in WHO-FC III PAH patients on background ERA therapy [67]. The

subsequent REPLACE trial showed benefit with switching stable intermediate risk patients from PDE5i therapy to riociguat (<https://pharmaceuticalbusiness-review.com/news/bayer-adempas-phase-4-trial/>).

Adverse effects were consistent between both trials, most commonly being headache, dyspepsia, dizziness, and hypotension. The latter is an adverse effect that is particularly unique to riociguat as compared to other oral therapies for PAH. The average mean arterial pressure reduction in both trials was 9 mmHg. Thus, riociguat requires slow up-titration to the target dose of 2.5 mg three times daily. It is typically started at 1 mg three times daily and increased by 0.5 mg three times daily at 2 week intervals if systolic blood pressure remains >95 mmHg. Of note, PDE5is and sGC stimulators should not be used in combination due to the duplication of the NO pathway and pronounced hypotension as evidenced in the PATENT PLUS trial [36]. Riociguat requires females to enroll in the Risk Evaluation and Mitigation Strategy (REMS) program due to the teratogenicity of the drug.

Endothelin Receptor Antagonists

Three ERAs are currently FDA-approved for the treatment of PAH. All three agents are teratogenic and require both prescribers and female patients to be enrolled in the REMS program. The REMS require females of reproductive potential to establish a negative pregnancy test prior to therapy initiation, monthly during therapy, and 1 month following therapy discontinuation. Additionally, bosentan carries an additional REMS program requirement of monthly liver function tests to monitor for hepatotoxicity. Bosentan is the only FDA-approved ERA for the pediatric population and is typically avoided in adults due to hepatotoxic risk. Other common adverse drug reactions for ERAs include edema, headaches, flu-like symptoms, nasal congestion, anemia, and urinary tract infection, in the setting of macitentan [21, 23, 30]. Doses for the following agents are as follows: bosentan 62.5–125 mg twice daily, ambrisentan 5–10 mg daily, and macitentan 10 mg daily. Doses for bosentan and ambrisentan are usually started low and titrated up as tolerated. Endothelin receptor antagonists are recommended in WHO-FC II–III patients [57].

Bosentan has been studied in a wide variety of trials and has been shown to improve cardiac index, PVR, patient-reported dyspnea, 6MWD, and TTCW [14, 24, 25, 27–29]. In the 24-week Study 351 trial, 32 patients with idiopathic or hereditary PAH or PAH associated with scleroderma were randomized to bosentan or placebo. All patients were WHO-FC III and were not on any PAH-specific medications at baseline. Patients on bosentan had a 70-m improvement in 6MWD from baseline as compared to a worsening of 6 m in the placebo group [24]. Bosentan continued to demonstrate improvements in WHO-FC III patients in the SERAPH, BREATHE-1,

and BREATHE-5 trials [14, 25, 27] and also showed benefit in WHO-FC II patients in the EARLY trial [28]. The COMPASS2 trial established additional benefits in patients already on stable doses of sildenafil [29]. Within the ARIES-1 and ARIES-2 trials, ambrisentan demonstrated improvements in 6MWD, TTCW, and WHO-FC at 12 weeks and at 48 weeks [22]. Macitentan showed favorable outcomes in TTCW, 6MWD, WHO-FC, and PAH-related death and hospitalization in WHO-FC II-III PAH patients, the majority of which were on concomitant PDE5i in the SERAPHIN trial [31]. In the 2017 MERIT-1 trial, macitentan was also found to reduce PVR and improve cardiac index and 6MWD in WHO-FC II-III CTEPH patients [32].

Parenteral and Inhaled Prostanoids

As the first class of PAH-specific therapies to become available, the prostanoid class came as a breakthrough therapy for this disease. All treatments prior to the FDA approval of epoprostenol were considered adjunctive or supportive therapies [57]. The prostanoid class is indisputably the most diverse class with agents available via oral, inhalation, IV, and subcutaneous (SQ) routes of administration (Fig. 1). The three parenteral and inhaled prostanoids are epoprostenol, treprostinil, and iloprost.

Parenteral prostanoids (i.e., epoprostenol, treprostinil) have maintained their role as the only class with a class I recommendation for WHO-FC IV patients [57]. Epoprostenol, the sole synthetic prostacyclin, is also the only PAH-specific therapy to have shown improved survival in a randomized, controlled trial [46]. The primary outcome of this 12-week trial, 6MWD, was improved by 31 m compared to placebo. Similarly, the stable prostacyclin analogue, treprostinil, showed 16-m 6MWD improvement as compared to placebo in its respective randomized, controlled trial [50]. Though this improvement in 6MWD may not seem impressive as an overall value when compared to what was shown with PDE5is or ERAs, two key factors must be taken into consideration. First, >90% of patients were WHO-FC III or IV at baseline between both trials, representing a population with much more advanced disease. Second, the mean dose achieved at 12 weeks was 9.2 and 9.3 ng/kg/min [46, 50]. In our experience, consistent with most practices internationally, maintenance doses of continuous infusion prostanoids are typically targeted to achieve doses of 40 ng/kg/min, or higher, as tolerated. Therefore, as serum concentrations are linearly increased at doses up to 125 ng/kg/min [48], coupled with further improvement as shown by Simmoneau and colleagues in patients in the highest quartile of treprostinil doses (i.e., >13.8 ng per kilogram per minute), larger increases in exercise capacity are anticipated at higher doses than mean doses achieved in the trials [50]. Epoprostenol and treprostinil are typically started at 1–2 ng/kg/min and titrated upward at 1–2 ng/kg/min every 12–24 h, as tolerated. The most common and dose-limiting adverse effects of parenteral

prostanoids during dose titration are headache, flushing, nausea, vomiting, jaw pain, diarrhea, abdominal pain, leg pain, arthralgias, myalgias, and hypotension. These occur during drug initiation and dose increases and typically resolve over time. Additionally, patients on SC treprostinil experience dose-limiting cutaneous site reactions due to a histamine-mediated response. This also resolves within 5–7 days maintained at a stable dose.

Given the need for continuous infusion of epoprostenol and parenteral treprostinil, the complexity of use of these agents cannot be overstated. First, all patients on chronic IV therapy require placement of an indwelling central venous catheter. Thus, patients must practice adequate line care hygiene to prevent the development of bloodstream infections [48]. Next, with a half-life of 3–5 min [44, 48], epoprostenol requires fairly capable and health-literate patients to be able to adequately manage a continuous infusion pump. The possibility of interruption in therapy and subsequent rebound PH resulting in death makes epoprostenol a very high-risk therapy [44]. Treprostinil, with a much longer half-life of approximately 4 h [48], allows more time for patients to reestablish access, making therapy interruption less of a concern and affords the ability to use continuous SC infusion. For patients on continuous SC treprostinil, maintenance of a viable infusion site requires considerable lifestyle modifications as they must continually keep the site dry and intact to maintain site longevity.

The recent introduction of an implantable infusion pump for treprostinil has garnered clinician and patient interest given fewer maintenance requirements by the patient and the ability to shower and swim without concern for getting the pump or the infusion site wet. Long-term studies of the use of the implantable pump have described cases of pump failure and pump pocket infections [68].

Inhaled therapies offer an alternative route for WHO-FC III-IV patients requiring a prostanoid. Iloprost, a prostacyclin analogue, and inhaled treprostinil, were both shown to improve 6MWD at 12 weeks [52, 54]. Though they obviate the need for central venous access and administration via a continuous infusion, both therapies are limited by frequency of dosing. Iloprost, dosed at 2.5–5 mcg six to nine times daily, requires around-the-clock administration at the target dose [53]. Though it requires less frequent administration, inhaled treprostinil still requires four administrations per day with a goal dose of 9 inhalations (54 mcg) four times daily [49]. Furthermore, the nebulization device required for inhalation of both agents is bulky and must be carried by the patient during any excursions outside of the home if >2 h for iloprost or >4 h for treprostinil. The dose-limiting side effects of inhaled therapies are similar to parenteral with the addition of cough and throat irritation shortly after drug administration [49, 53].

Prostanoid Prescribing and Management Considerations

Oral / Inhaled Prostanoids				IV / SQ Prostanoids				
- Typically indicated in WHO-FC II-III; consider in WHO-FC IV patients deemed poor IV/SQ candidates				- Treatment of choice in WHO-FC IV & typically started inpatient				
- Specialty pharmacy nursing available at initiation of therapy and at prescriber specified intervals				- Specialty pharmacy nursing support limited to pump management				
				- Must have available support person and accommodating social environment				
				- Potential risk with abrupt discontinuation				
Oral Prostanoids		Inhaled Prostanoids		Epoprostenol and Treprostinil				
Selexipag		Treprostinil		Iloprost		Treprostinil		
Dosing	Starting dose: 200 mcg BID Titrate by 200 mcg weekly up to 1600 mcg BID	Starting dose: 0.125 mcg TID Titrate by 0.125 mg no more frequently than every 3-4 days to max tolerated dose	Starting dose: 2.5 mcg 6-9 times daily Titrate up to 5 mcg 6-9 times daily	Starting dose: 3 breaths QID Titrate by 3 breaths weekly up to 9 breaths QID				
Prescribing Pearls	-Anticipate extended prior authorization turnaround times with initial drug approval -Complex prior authorizations due to varying dosages -BID dosing of selexipag may be preferable over TID treprostinil -Successful transitions to-and-from IV, SQ, inhaled, oral prostanoids ¹² -Selexipag has fewer titration steps than treprostinil		-Anticipate extended prior authorization turnaround times with initial drug approval -Potentially less out-of-pocket cost compared to oral prostanoid therapy -Must carry inhalation system for dosing -High treatment burden: requires daily preparation, administration, and cleaning		Starting dose: 1-2 ng/kg/min Increase by 1-2 ng/kg/min every 12-24 hours while inpatient; as an outpatient, increase by 1-3 ng/kg/min every 24-72 hours with cartridge changes as tolerated to a therapeutic goal of at least 30-40 ng/kg/min			
					Epoprostenol		Treprostinil	
					IV (+ diluent) -Half life: 3-5 minutes -Generic and branded Flolan are only stable for up to 8 hours at room temperature following mixing (up to 24 hours with cold packs) -Branded Veletri is stable for longer periods at room temperature following mixing -Premixed solution is available in some geographic areas at certain stable doses -Recommend tunneled line with dedicated single lumen -Take strict precautions (e.g. warnings signs, labelling the line, etc.) to avoid accidental bolus injection -Significant risk of central line infection; impeccable central line care is paramount		-Half life: 4 hours (longer half life allows for additional time to access care if therapy is interrupted)	
							IV (+ diluent) -Generic available -Requires mixing -Premixed solution is available in some geographic areas for patients on a stable dose of treprostinil -Recommend tunneled line with dedicated single lumen -Take strict precautions (e.g. warnings signs, labelling the line, etc.) to avoid accidental bolus injection -Significant risk of central line infection; impeccable central line care is paramount	
Side Effect Management	-Anti-diarrhea therapies: diphenoxylate/atropine, loperamide -Anti-nausea therapies: promethazine, ondansetron, prochlorperazine -Pain management: acetaminophen often used		-Cough may be mitigated by lozenges and frequent mouth rinsing -Review inhalation technique: breaths are gentle, unlike customary inhalers -Treprostinil: may need to slow up-titration to a single breath at a time to improve tolerability		SQ (no diluent) -Site irritation is common; site pain may be intolerable -Generic is available but SQ pump is currently licensed for branded Remodulin only, thereby limiting utility of generic therapy -Decreased infection risk compared to IV -Cartridge changes are less complex than IV -Outpatient initiation feasible but not routine			
	Dose titration tips -May need to slow up-titration to improve tolerability -May require additional insurance authorization for starter and titration packs or varying dosages -Can consider trying to increase dose again once symptoms become tolerable -Selexipag: if side effects persist, consider increasing PM dose first, then increasing AM dose once PM dose is well-tolerated -if side effects persist, consider taking with food or increasing caloric intake and protein content				Important considerations before prescribing: -Confirm availability of a support person: requires a 2-person check system to maintain sterile fields, manage infusion pump, care for infusion site, & ensure successful & safe infusion therapy -Consider home environment, social circumstances, patient's and support person's dexterity, and likelihood of compliance, especially in patients with a history of substance abuse -Initiation involves intensive teaching of both the patient and the support person; both should demonstrate independence in preparing and administering parenteral therapy -Recommend using IBW for consistent dosing weight throughout therapy -Local emergency rooms, EMS, and inpatient hospital units welcome educational sessions and materials, as well as available PH expertise, to assist in managing patients on parenteral prostanoid therapy			
					-Confirm availability of a support person: requires a 2-person check system to maintain sterile fields, manage infusion pump, care for infusion site, & ensure successful & safe infusion therapy -Consider home environment, social circumstances, patient's and support person's dexterity, and likelihood of compliance, especially in patients with a history of substance abuse -Initiation involves intensive teaching of both the patient and the support person; both should demonstrate independence in preparing and administering parenteral therapy -Recommend using IBW for consistent dosing weight throughout therapy -Local emergency rooms, EMS, and inpatient hospital units welcome educational sessions and materials, as well as available PH expertise, to assist in managing patients on parenteral prostanoid therapy			
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Fig. 1 Prostanoid prescribing and management considerations. EMS, emergency medical services; IBW, ideal body weight; PH, pulmonary hypertension; WHO-FC, World Health Organization Functional Class

Oral Prostanoids

There are numerous challenges to both parenteral and inhaled prostanoid formulations, which require additional resources, time, and education for safe and effective use of these therapies. For these reasons, an oral formulation serves as an attractive alternative. Nearly 20 years after the introduction of IV epoprostenol, the FDA approved oral treprostinil diolamine in an extended release formulation [39]. However, treprostinil diolamine uptake in clinical practice has been limited, in large part due to mixed results in the literature. In the FREEDOM M trial, treprostinil monotherapy in treatment-naïve, WHO-FC II-III PAH patients significantly improved 6MWD [42]. Conversely, in patients already receiving background PAH therapies, oral treprostinil failed to show significant improvement in 6MWD or TTCW in both the FREEDOM C [40] and FREEDOM C2 [41] trials. In the FREEDOM C and FREEDOM C2 trials, approximately 45% and 40% of patients, respectively, were on both an ERA and PDE5i at baseline. More recently, in the 2019 FREEDOM-EV trial, oral treprostinil significantly decreased time to first clinical worsening event by 26% compared to placebo in patients who were recently diagnosed with PAH (median of 6.4 months) and on monotherapy PDE5i or ERA at baseline [43]. The treatment difference was driven by delayed disease progression. On the whole, the evidence for the use of oral treprostinil is conflicting, and its place in clinical practice remains unclear, particularly without any distinctive benefit in the contemporary setting, where upfront combination therapy is now the standard of care.

The recommended starting dose for treprostinil diolamine is 0.25 mg twice daily or 0.125 mg three times daily and is typically increased every 3–4 days as tolerated [39]. Three times daily dosing is preferred in order to avoid large swings in serum drug levels. A large peak:trough ratio may result in increased adverse effects and limit the max daily dose achieved. Furthermore, patients may also experience prolonged periods at low drug levels [69]. Common adverse effects include diarrhea, headache, nausea, flushing, jaw pain, fatigue, and myalgias [39, 70]. Strategies to improve drug tolerability and cut down on the severity of dose-limiting side effects include [1] three times daily dosing; [2] dose titration in increments no greater than 0.125 mg, which can be initiated with one dose first (usually the evening dose); and [3] extending the intervals between dose titrations to allow patients more time to acclimate to the effects of the medication [69] (Fig. 1). The oral bioavailability of treprostinil diolamine is ~17% and should be administered with a 250-cal meal containing 30–50% fat to enhance drug absorption [71]. As with other PAH-specific therapies, abrupt discontinuation of treatment should be avoided. The dose may be reduced in increments of 0.5–1 mg per day, with consideration for tablet strength, as tablets may not be cut or crushed [39].

The other orally available agent targeting the PGI₂ pathway, selexipag, received FDA approval in 2015. Selexipag is a selective prostacyclin receptor (IP receptor) agonist [37, 72] recommended for use in WHO-FC II-III PAH patients [57]. In the 2015 GRIPHON trial, the primary endpoint of morbidity and mortality occurred in significantly fewer patients on selexipag compared to those in the placebo arm. Study patients were predominantly WHO-FC II-III and on concomitant ERA and/or PDE5i therapy. The treatment effect was driven primarily by disease progression and hospitalization as a result of worsening PAH. 6MWD was also notably improved in the selexipag group. However, selexipag did not significantly reduce all-cause mortality [38].

The starting dose of selexipag is 200 mcg twice daily. This is typically increased by 200 mcg twice daily at weekly intervals to the highest dose tolerated by the patient up to a maximum dose of 1600 mcg twice daily. Common adverse effects include headache, diarrhea, nausea, flu-like symptoms, and flushing [37]. These side effects typically subside with time and may require increasingly longer periods of adjustment as the doses get higher. A single-dose step-up method may also be implemented for patients experiencing difficulty with dose titrations, where the evening dose is increased first before increasing the morning dose a week later. The expectation for maximally tolerated doses should not be that side effects subside completely, but rather the dose at which the patient experiences side effects that are manageable. Side effect management strategies vary by center (Fig. 1). Once the side effects become intolerable or unmanageable, the dose is decreased by 200 mcg twice daily and parked. This dosing strategy stems from the GRIPHON trial, which saw all maximally tolerated doses demonstrate similar efficacy for the composite primary endpoint.

Ralinepag is another selective IP receptor agonist currently undergoing phase 3 clinical trials (<https://clinicaltrials.gov/ct2/show/NCT03626688>). In the phase 2 clinical trial, ralinepag significantly reduced PVR in PAH patients on background PAH-specific therapies [73]. The extended-release formulation being tested in the ongoing phase 3 trial provides the advantage of once daily dosing. Phase 3 study results are expected in 2021–2022 (<https://clinicaltrials.gov/ct2/show/NCT03626688>).

Combination Therapy

As our understanding of PAH further develops, coupled with expanding research, development, and clinical experience with novel PAH-specific therapies, the paradigm for the optimal management of PAH has shifted in recent years. Combination therapy, targeting the NO, ET-1, and PGI₂ pathways, has emerged as the contemporary standard of care in treatment of PAH patients. Historically, combination therapy was implemented in a sequential method based on baseline

and subsequent FC, as well as hemodynamic assessments. The AMBITION trial, published in 2015, was a randomized, controlled trial in WHO-FC II-III PAH, treatment naïve patients comparing combination therapy with tadalafil 40 mg daily and ambrisentan 10 mg daily versus tadalafil or ambrisentan monotherapy. The primary endpoint was the first event of clinical failure, time to clinical failure (TTCF), defined as the first occurrence of a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. Patients started on combination therapy had a significantly longer TTCF (HR 0.50, 95% CI: 0.35–0.72; $p < 0.001$) [20]. The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines assigned class I recommendations for combination therapy with the following: macitentan and sildenafil (based on the SERAPHIN trial) [31], riociguat and bosentan (based on the PATENT-1 trial) [34], and selexipag and PDE5i or ERA therapy (based on the GRIPHON trial) [38]. Other dual therapy combinations were given a lower level of evidence recommendation [57].

However, despite a decrease in TTCW, many patients continue to experience worsening symptoms, clinical deterioration, and limited functional status. This has naturally given way to exploring the effects of triple combination therapy on patient outcomes. Three main studies have looked at triple therapy. The first trial, a small pilot study of 19 patients, initiated combination therapy with IV epoprostenol, bosentan, and sildenafil. Overall, the patients had improvements in 6MWD, hemodynamics, FC, and survival [74]. Secondly, the GRIPHON trial demonstrated benefit in adding on selexipag to ERA and PDE5i background therapy [38]. In the GRIPHON trial, 14.7% of patients were on PDE5i monotherapy, 32.4% on ERA monotherapy, and 32.5% on both ERA and PDE5i therapy. Within the pre-specified subgroup analysis, the benefit in the primary outcome was still present within the dual therapy group [38]. Thirdly, the TRITON trial provides more information regarding combination therapy (<https://clinicaltrials.gov/ct2/show/NCT02558231>). The TRITON study is a multicenter, double-blind, placebo-controlled, phase 3b study with newly diagnosed, treatment-naïve PAH patients randomized to upfront triple or initial double therapy. Macitentan and tadalafil were initiated at randomization, and selexipag or placebo was added at day 15 (and subsequently uptitrated until week 12). The primary endpoint was change in PVR at week 26. Initial triple and initial double therapy reduced PVR by 54% and 52%, respectively, with no difference between the groups. In addition, both groups saw improvement in 6MWD and NT-proBNP, as well as no worsening in FC, with no difference between groups. Discontinuation rates due to adverse effects were similar between the initial triple and initial dual combination groups (https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A2928). This

raises concern about the role and value of upfront initial triple combination therapy in Group 1 PAH.

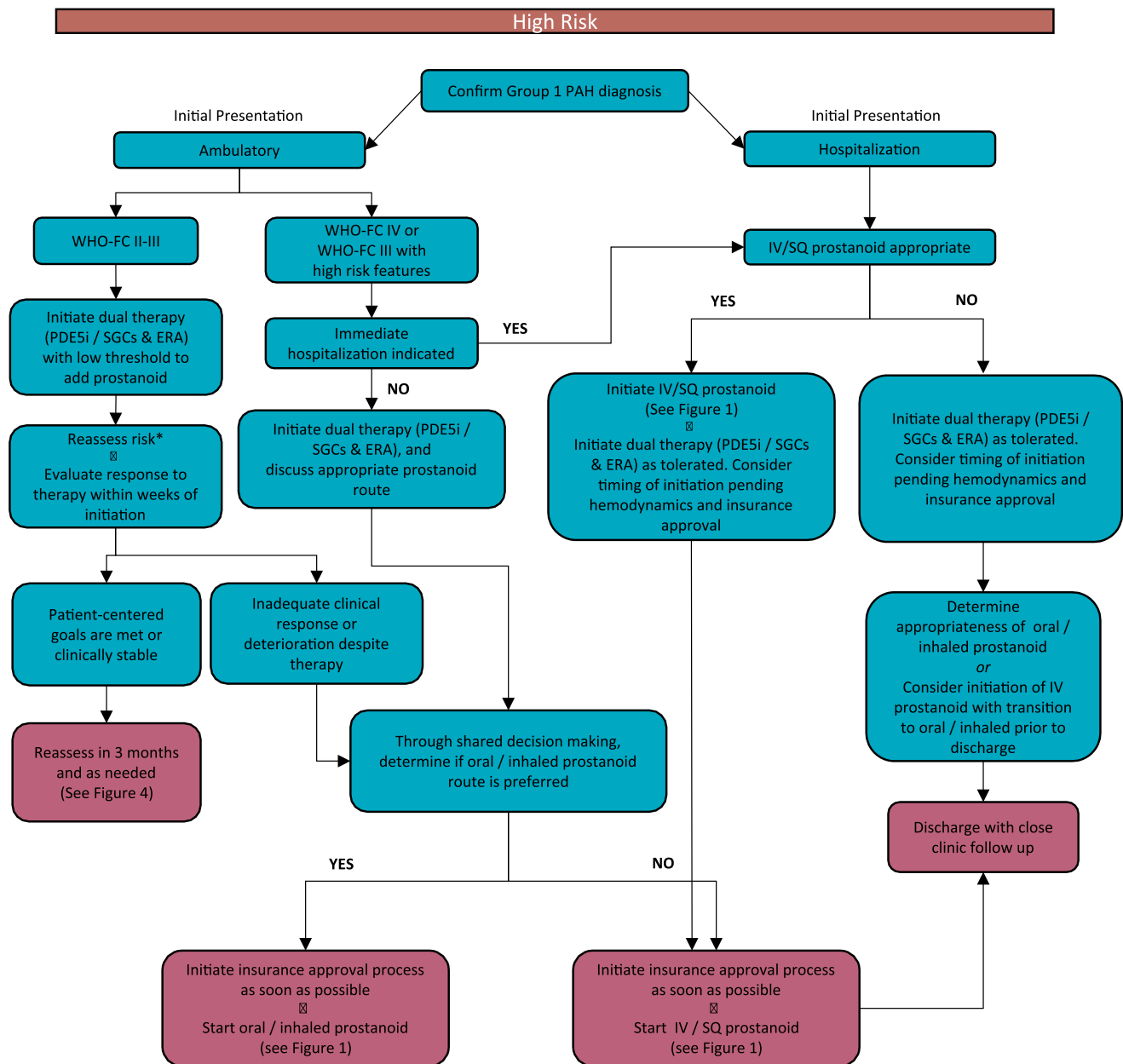
As the body of evidence for combination therapy grows, it is important to consider individualized strategies to achieve adequate combination therapies while minimizing adverse side effects that may lead to therapy discontinuation (Fig. 1). Some of these strategies include staggered therapy initiation and dose titrations, frequent monitoring, and aggressive management of adverse drug reactions [75]. It is essential for clinicians to adapt and tailor recommendations as more data becomes available and to determine the optimal approach to the pharmacologic management of PAH.

Personalizing Pulmonary Arterial Hypertension Therapies

When determining the optimal therapeutic approach for PAH patients, there are several best practice guidelines from the ESC/ERS, CHEST, and the World Symposium of Pulmonary Hypertension (WSPH) [6, 57, 76]. Risk is routinely assessed through ESC/ERS and REVEAL 2.0 risk calculators with therapies tailored accordingly [57, 77]. There are currently 14 FDA-approved therapies in the USA, and therapeutic changes may be appropriate months to years after initiation to accommodate clinical status and patient-specific needs.

Once an accurate assessment of all PH risks has been completed, appropriate diagnostic tests have been performed, and WHO Group 1 PAH confirmed, a determination should be made as to whether the patient is high, intermediate, or low risk (Figs. 2 and 3). The ESC/ERS and REVEAL 2.0 risk categorization guides are frequently used to guide initial therapy class choices [57, 77]. These risk assessments include clinical evaluation for signs of right heart failure, WHO-FC assessment, laboratory values (viz., NT-proBNP levels), imaging findings, and hemodynamics, in addition to the etiology of PAH.

For a new diagnosis of PAH, the 6th WSPH recommends upfront dual combination therapy with an ERA and PDE5i [76]. Although preferable, simultaneous initiation of an ERA and PDE5i can be challenging. Many programs initiate a PDE5i, and within a few days or weeks, rapidly initiate an ERA if upfront dual combination therapy is not feasible (Fig. 3). Follow-up visits should be scheduled within weeks of therapy initiation to discuss any side effects, as well as provide an opportunity to review the disease state, questions, management of comorbidities, and other supportive measures such as oxygen and diuretics. REMS considerations, if applicable, should also be reviewed. Separating the initiation of a PDE5i and an ERA, even by a few days, often not only helps to facilitate insurance approval of the ERA but also helps to identify adverse effects from a specific therapy. If a PDE5i is



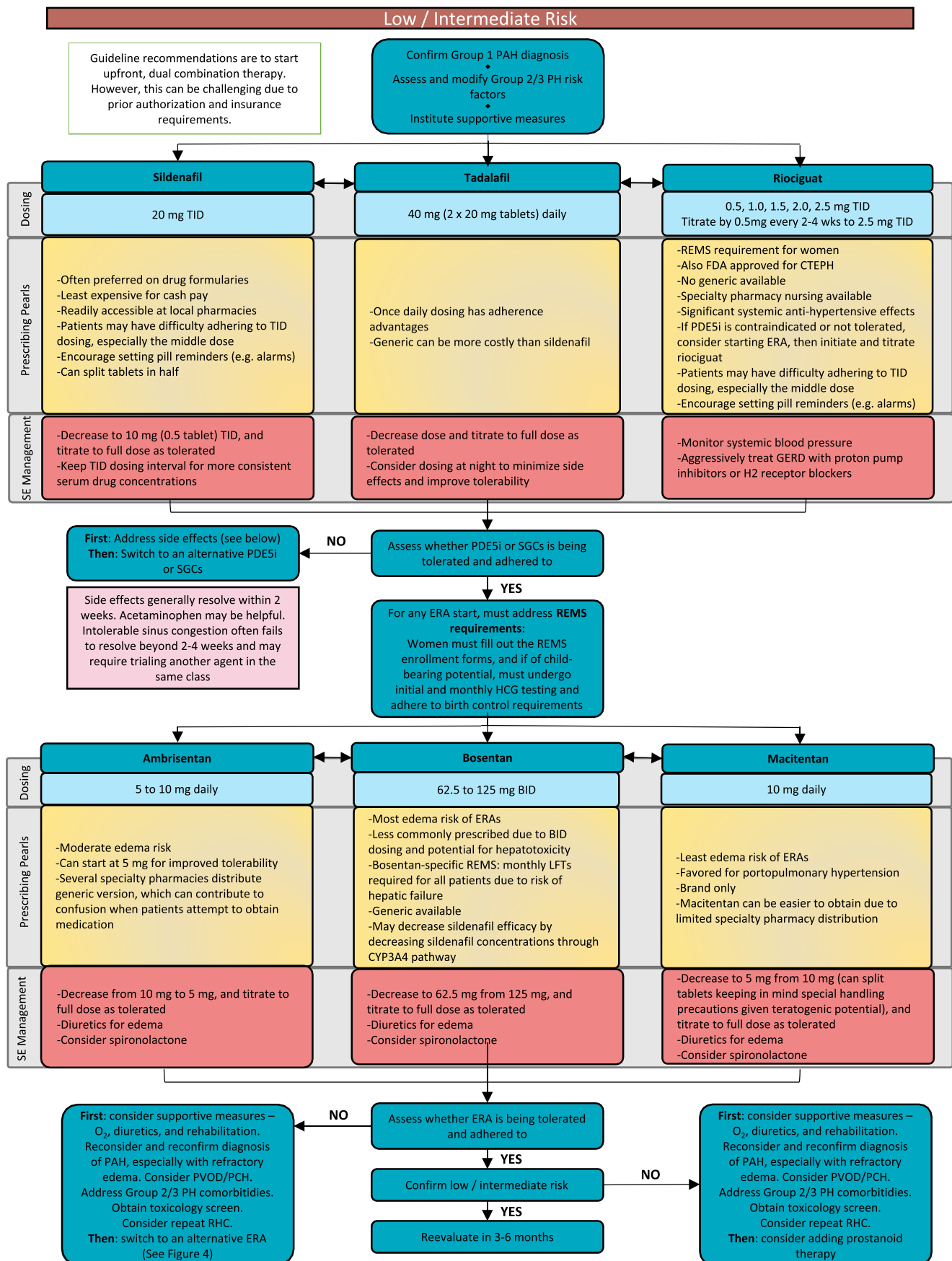
*Risk assessed using the 2015 ESC/ERS Risk Assessment in PAH and REVEAL 2.0 risk score

Fig. 2 Management of high-risk PAH patients. bid, twice a day; ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension;

PRN, as needed; SGCs, soluble guanylate cyclase stimulator; tid, three times a day; qid, four times a day; WHO-FC, World Health Organization Functional Class

not tolerated or is contraindicated, riociguat is preferred and will require additional time for titration. In addition, it may be reasonable to switch from a PDE5i to riociguat in patients who remain at intermediate risk based on the REPLACE trial (Fig. 3) (<https://pharmaceutical-business-review.com/news/bayer-adempas-phase-4-trial/>).

In a low-to-intermediate risk patient on combination therapy, reassessment within 3 months is preferred to evaluate goals, functional response to therapy, and possible need for prostacyclin therapy (Fig. 4). It is important to continually reassess diagnosis and other risk factors for PH, ensure comorbidities are optimally managed, and review medication



◀ **Fig. 3** Management of low-intermediate risk PAH patients. bid, twice a day; ERA, endothelin receptor antagonist; FDA, Food and Drug Administration; GERD, gastro-esophageal reflux disease; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; REMS, risk evaluation and mitigation strategy; RHC, right heart catheterization; SGCs, soluble guanylate cyclase stimulator; tid, three times a day; WHO-FC, World Health Organization Functional Class

compliance, especially if patients lack subjective or objective improvement on dual therapy (Table 4). In a high risk but stable patient, as often indicated by first visit in an ambulatory setting as opposed to the hospital, dual combination therapy is rapidly initiated. Using shared decision-making considers the preferred route of prostanoid therapy early on in the care of the patient. When initiation of a parenteral prostanoid is indicated, prescribing considerations include geographic distance from their PAH care center, social circumstances including availability of support person, patient dexterity, and risk profile for infection.

Patient tolerability, both physically and financially, should be considered. In the USA, we remain subject to insurance formularies, hospital availability, and patient cost sharing. Clinicians play an important role in advocating on behalf of patients for insurance approval of PAH-specific therapies (Table 5). However, this requires dedication of additional time and resources and more importantly, can delay time to

initiation of therapy for up to a month or more. Each patient case should be individualized according to the risk assessment, medication preference (taking into consideration comorbidities), and potential cost hurdles based on experience with insurance formularies.

Interventional Strategies for Pulmonary Arterial Hypertension

While pharmacotherapy remains the cornerstone of treatment, PAH remains a progressive, fatal disease with a fair amount of heterogeneity in response to pharmacotherapy [78]. Several non-pharmacologic options have been explored as adjunct therapies and have shown improvement in hemodynamics and quality of life in high risk PAH populations in small clinical experiences [79–82]. However, given the lack of data surrounding these techniques, non-pharmacologic therapies discussed in this section are largely considered palliative or a bridge to transplantation at this point.

Atrial Septostomy

Balloon atrial septostomy involves the creation of a right-to-left shunt using percutaneous balloon dilations across the interatrial septum, reducing right ventricular pressure and volume. This consequentially increases cardiac output which augments systemic oxygen transport despite decreasing systemic oxygen saturation [80, 83]. The idea behind creation of an interatrial shunt dates back to the 1980s when patients with patent foramen ovale and PAH with resultant right-to-left shunting were noted to have improved survival compared to those without shunting [84]. Decades following this discovery, the precise role for atrial septostomy remains uncertain, and data regarding its use largely comes from small case series and case reports. The most recent data available suggests a hemodynamic and symptomatic benefit in patients with WHO-FC IV symptoms due to right sided heart failure despite optimal pharmacologic therapy [80, 82, 85]. In this patient population, patients were noted to have increased cardiac index, decreased right atrial pressure, and improvement in 6MWD following atrial septostomy. However, the impact of atrial septostomy on long-term survival has not been established, and current guidelines recommend considering atrial septostomy only as a palliative or bridging measure in experienced centers [86]. Furthermore, baseline right atrial pressures of > 20 mmHg or resting arterial oxygen saturations < 85% are contraindications to atrial septostomy due to the hemodynamic alterations that occur following the procedure.

Table 4 Special Considerations in Treatment Selection of PAH

Continually reassessing WHO Group 1 PAH vs. other WHO Group PH risks and management remains important to patient-centered care (especially in those with overlapping cardiac and/or lung disease).
Monotherapy may be appropriate for some.
Patients should be counseled that PAH-specific therapies oftentimes do not immediately improve symptoms or functional status and may take weeks or months to notice improvement.
Oxygen, diuretics, and other supportive therapies remain important in reaching low risk status.
Vasoreactivity should always be assessed when appropriate (i.e., idiopathic, familial, or drug/toxin-induced PH), and CCB therapy initiated as indicated.
A more convenient therapy does not always equate to improved tolerability.
Side effects of one medication within a drug class may not be as frequent or severe with another medication within the same therapeutic class.
Connective tissue disease patients often have overlapping interstitial lung disease. Use extra caution and monitor closely for side effects and deterioration with vasodilators.
Toxin-induced patients, particularly those currently using methamphetamines, may struggle with medication compliance and adherence to REMS requirements.
Initiation of medications with REMS requirements need to be carefully considered, particularly in women of child-bearing potential and the ability to reliably perform monthly pregnancy testing.

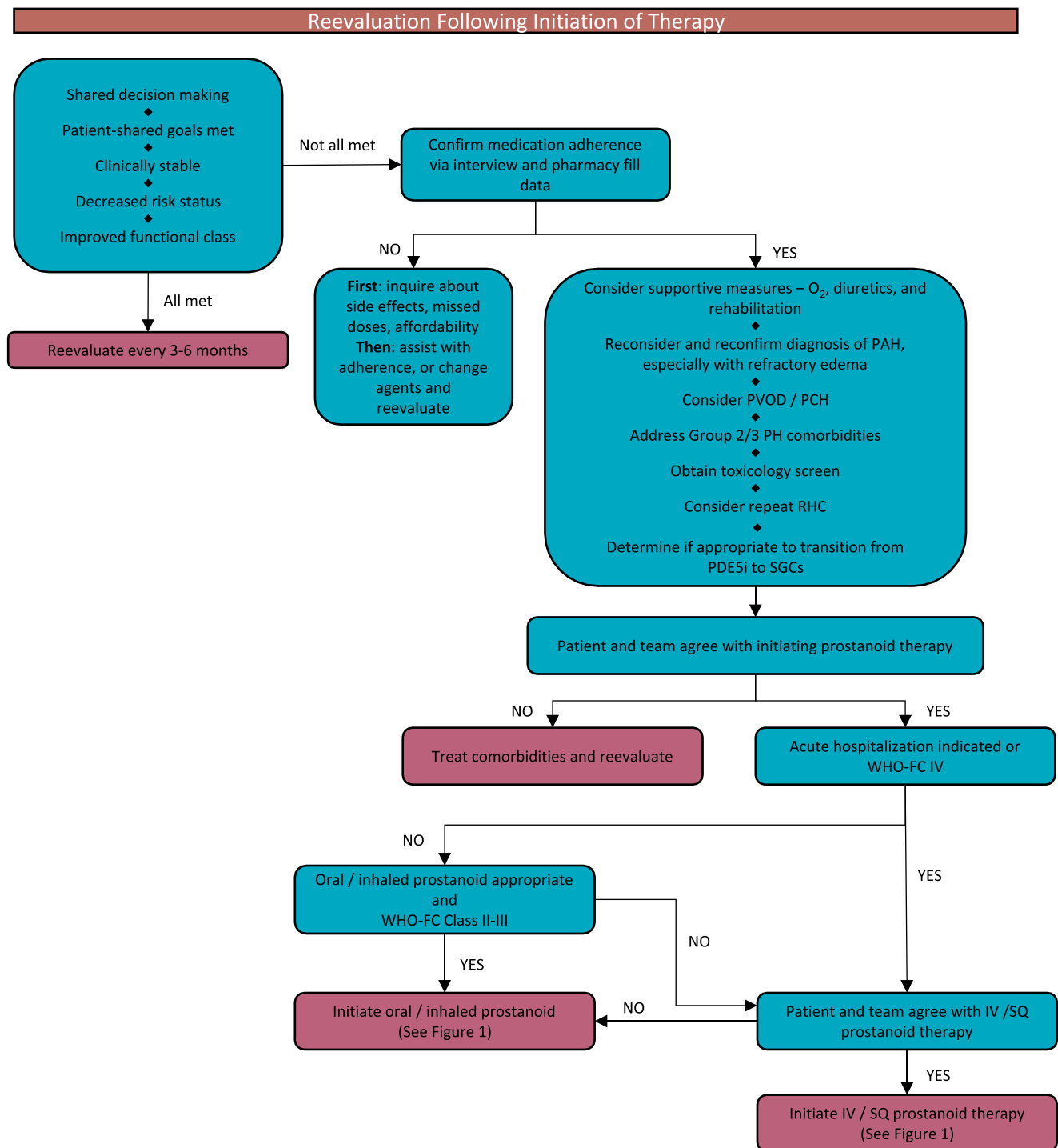


Fig. 4 Reevaluation of patients with PAH after initiation of therapy. PAH, pulmonary arterial hypertension; PH, pulmonary hypertension;

PVOD, pulmonary veno-occlusive disease; RHC, right heart catheterization; WHO-FC, World Health Organization Functional Class

Potts Anastomosis

Initially described decades ago for the management of certain congenital heart diseases, a Potts anastomosis/shunt involves a surgical anastomosis of the left pulmonary artery to the descending aorta via a left thoracotomy. More recently, a technique for transcatheter Potts shunt creation was also described,

though data regarding this approach is sparse [87]. A Potts shunt creates a right-to-left shunt that theoretically avoids arterial oxygen desaturation above the level of the anastomosis, sparing cerebral and coronary circulation. Thus far, the most robust evidence for Potts shunting as an adjunctive treatment in PAH is in children. A small case series of 24 children undergoing surgical Potts anastomosis (ages 1.5–17 years)

Table 5 Financial considerations that impact treatment options in PAH**Insurance specific**

- Prior authorization is required in most cases. A comprehensive progress note facilitates faster approvals. The progress note should include:
 - WHO Group
 - Functional Class
 - Current PAH therapy regimen
 - PAH therapies tried and failed with approximate dates
 - Right heart catheterization results including vasoreactivity assessment
 - Rationale for PAH-specific therapy if risk factors for other WHO Group PH exist
- Therapies often may only be filled at a specific specialty pharmacy or may be less expensive at payer-preferred pharmacies which can be less convenient

Medication cost

- Medication price is often not readily available to prescribers and may first require prior authorization and then coordination with pharmacy and/or insurance to assess affordability
- Generics may cost more out-of-pocket if a copay card is available through the branded drug manufacturer
- Copay cards offered by drug manufacturers are restricted to commercial patients only (cannot be used with Medicare, Medicaid, Tricare, etc.)
- Encourage patient to consider total yearly out-of-pocket costs as monthly expenses may fluctuate throughout the year and satisfy various insurance structures including:

- Annual deductibles
- Maximum out-of-pocket for commercial insurance
- Coverage gap (i.e., donut hole) and catastrophic coverage for Medicare Patient assistance (primarily based on financial need)

- Additional financial support may be available and requires patient effort and initiative. Often entails formal income and residency verification. Examples include:

- Non-profit grants primarily for Medicare patients
- Manufacturer assistance for branded therapies if grants are not available
- Specialty pharmacy assistance in select cases (patient must ask pharmacy)
- Uninsured patients or those who have received an insurance denial and subsequent appeal denial for a branded therapy for an FDA-approved indication may qualify for patient assistance through the manufacturer at zero cost

with drug-refractory PAH showed improvement in WHO-FC, 6MWD, and NT-proBNP levels with no further worsening of right ventricular function (median follow-up of 2.1 years) in the 21 patients who survived the procedure [88]. While early experience with this technique is promising in small case series, further understanding and refinement of patient selection criteria are warranted to establish the role of Potts shunting as a therapeutic modality in PAH.

Pulmonary Artery Denervation

Similar to renal denervation for systemic hypertension, modification of sympathetic pulmonary innervation has been proposed as a potential target for pulmonary arterial hypertension therapy. While results from animal models demonstrating the role of sympathetic tone in pathogenesis and as a potential target for intervention have been promising, relevance to human disease

remains unproven [89, 90]. A first-in-man, single center study of 13 patients undergoing pulmonary arterial denervation demonstrated significant reduction in mean PAP, NT-proBNP, and improvement in 6MWD, pulmonary arterial compliance, and functional capacity compared to a control group at 3 months [91]. Additionally, no major complications of the procedure were reported. In the multicenter, open-label TROPHY trial, intravascular ultrasound pulmonary artery denervation decreased PVR and was associated with an improved 6MWD [92]. While these results are encouraging, further investigation and confirmation of these findings are required before this strategy can be adopted into clinical practice.

Atrial Septal Defect Closure

Atrial septal defects (ASDs) are among the most common of congenital heart diseases, and PAH has been associated with ASDs in 4–34% of patients [93, 94]. Based on the most 2018 AHA/ACC guideline for the management of adults with congenital heart disease, closure of an ASD is currently indicated to reduce right atrial and right ventricular pressure/volume if there is evidence of right-sided enlargement and net left-to-right shunting with pulmonary-systemic blood flow ratio ($Q_p:Q_s$) ≥ 1.5 , provided the PAP is less than 50% of systemic blood pressure and PVR is less than one-third of the systemic vascular resistance (Class I, Level of Evidence B) [95]. Closure of an ASD in adults with PAP greater than two-thirds systemic pressure, PVR greater than two-thirds systemic, or net right-to-left shunting is not recommended (Class III, level of evidence C) [95]. However, there are no set guidelines regarding atrial septal defect closure in the presence of net left-to-right shunting with PAP or PVR between one-half and two-thirds systemic pressure or resistance [95]. Despite the lack of conclusive data, pulmonary vasodilator testing is generally recommended in this scenario for patients with a baseline pulmonary vascular resistance index (PVRI) of 6–9 WU*m2. A 20% decrease in PVR, a 20% decrease in pulmonary vascular resistance:systemic vascular resistance (PVR:SVR) ratio, a final PVRI < 6 WU*m2, and final PVR:SVR ratio $< 33\%$ with vasodilator challenge likely indicate a favorable response after atrial septal defect closure, though this is largely based on small case series and expert consensus [96].

Surgical Management of Pulmonary Arterial Hypertension

Indications for Lung Transplant

While medical therapies for PAH have made great strides in recent years, lung transplantation remains an important therapy for patients with severe disease refractory to medical therapy. Although transplantation for PAH is a relatively rare indication (~5% of all lung transplants) compared to COPD

or interstitial lung disease, referral is appropriate when the patient's predicted 2–3-year survival is estimated to be < 50% [57]. Perioperative risk is minimized with early referral before severe cardiac dysfunction and hepatic congestion develop. Widely accepted criteria for the referral for transplant evaluation consist of the following:

- WHO-FC III of IV symptoms despite maximal medical therapy
- A markedly low (< 350 m) or declining 6MWD
- Cardiac index of < 2 L/min/m²
- Central venous pressure ≥ 15 mmHg

Listing for lung transplantation is appropriate with deterioration of functional status and hemodynamics. Not all patients with PAH, however, are candidates for transplantation, and the usual contraindications (active/recent malignancy, substance abuse, poor social support, non-adherence) still apply. Since 2005, organs in the USA have been allocated under a new system called the Lung Allocation Score, or LAS. It serves as a severity of illness score ranging from 0 (well) to 100 (ill). The LAS weighs the probability of death in 1 year without transplant against the probability of death 1 year posttransplant. The purpose of implementing the LAS was to decrease deaths on the wait list, and it lowered wait-list mortality for all etiologies of lung failure except PAH. These changes relatively disadvantaged patients with PAH from getting an organ with some evidence of increased wait-list mortality [97, 98]. This led to LAS exceptions relating to evidence of worse prognosis, specifically cardiac dysfunction (elevated central venous pressure and/or low cardiac index) [98].

Type of Transplant and Results

The overwhelming majority of patients receiving lung transplantation for PAH receive bilateral lung transplants (BLT) rather than single lung transplants (SLT), although the evidence to support this practice is fairly weak. Proponents of SLT cite the benefits of lower perioperative morbidity, improved graft function, and more equitable organ allocation, while proponents for BLT argue for possible improved long-term survival, and patients are easier to manage in both the early and late term due to less V/Q mismatching. Despite the controversy, the overwhelming majority of patients (91%) with PAH receive BLT with good results [99]. Heart-lung transplantation is an option for patients with end-stage PAH and severe cardiac dysfunction. It is usually reserved for patients with PAH related to congenital heart disease and represents < 2% of lung transplants [99]. In general, patients with PAH have higher perioperative risks, and conditional survival (at 1 year) is superior to COPD and interstitial lung disease.

Future Directions in Pulmonary Arterial Hypertension Management

As previously stated, currently available therapies for treating PAH target endothelial cell dysregulation and smooth muscle cell tone and proliferation through three mechanistic pathways: the ET-1 pathway, the NO pathway, and the PGI₂ pathway [1, 100]. However, pathologic mechanisms leading to the characteristic histologic findings and dysfunctional pulmonary vascular endothelium in PAH are complex and include dysregulated inflammation with immune activation, oxidative stress, an imbalance of proliferative and anti-proliferative signaling, growth factor activation, dysfunctional metabolism, and altered hormonal signaling [101, 102]. Recent efforts have focused on exploiting the multiple mechanisms leading to pulmonary vascular remodeling seen in PAH to develop novel therapeutics. Various pathways for target include suppressing inflammation and modulating the immune response, altering oxidant stress mechanisms, restoring the balance between pro-proliferative and antiproliferative signaling, and targeting growth factor signaling pathways pertinent to BMPR2 regulation [101, 103, 104].

Sustained inflammation and immune activation lead to increased cytokine and chemokine production with subsequent perivascular infiltration of macrophages, granulocytes, mast cells, dendritic cells, B and T lymphocytes, and natural killer T cells [101]. There is evidence that the presence of soluble factors and cell surface molecules (i.e., IL-1, IL-6, TNF- α , CRP, and MCP-1) and activation of signaling pathways play critical roles in promoting vascular remodeling, portend a worse prognosis, and may serve as biomarkers of disease progression or, importantly, future therapeutic options [105–110]. Recent studies have examined anakinra and tocilizumab, IL-1 and IL-6 receptor antagonists, respectively, for their use in PAH. The safety and feasibility of anakinra was investigated in a small, single-arm open label study [111]. Although the study was not designed to show improvement in clinical or functional outcomes, the authors were able to demonstrate nonsignificant improvements in clinical heart failure symptoms, lower IL-6 levels, and an inverse relationship between high sensitivity C-reactive protein levels and peak oxygen consumption. Tocilizumab was also shown to be a safe and feasible treatment option in PAH patients and demonstrated reduced C-reactive protein levels but failed to show a treatment effect in any of the measured clinical endpoints in a small exploratory open-label study [112]. These authors were able to provide clear proof of principle, safety, and feasibility data that support conducting future studies with a focus on clinically meaningful endpoints. Plasmablasts in idiopathic PAH have shown clonality similar to that observed in autoimmune diseases, and the CD-20 antibody, rituximab, has been studied for safety and efficacy of B cell depletion in systemic sclerosis associated-PAH; the safety profile was promising, and there were trends toward clinical improvements [113, 114].

Mitochondrial generation of reactive oxygen species have been implicated in the development of PAH; inhibition of oxidative stress mechanisms has been proposed to attenuate pulmonary vascular remodeling seen in PAH [115, 116]. Bardoxalone methyl activates Nrf2, a transcription factor that regulates the expression of antioxidant proteins and suppresses the activation of the pro-inflammatory NF κ B pathway, and has shown promising results. In the multicenter, phase 2 LARIAT trial, patients with PAH on stable background therapy and WHO-FC II or III were assigned to bardoxalone methyl or placebo (<https://clinicaltrials.gov/ct2/show/NCT02036970>). After 16 weeks of therapy, there was a significant improvement 6MWD in the treatment group as compared to the placebo group. The follow-up CATALYST and RANGER were discontinued during the COVID19 pandemic, and it was noted that bardoxalone was unlikely to meet its primary endpoint in the study (6MWD) (<https://clinicaltrials.gov/ct2/show/NCT02657356>, <https://clinicaltrials.gov/ct2/show/NCT03068130>, <https://pulmonaryhypertensionnews.com/2020/04/01/reata-stops-pah-bardoxalone-trials-amid-covid-19-concerns/>).

Impaired BMPR2 signaling is the most common genetic mechanism implicated in PAH and contributes to the development of pulmonary vascular disease through exaggerated TGF- β signaling [117]. Because the BMPR2 receptor is a TGF- β receptor subtype, targeting TGF- β signaling with sotatercept, an activin receptor type 2A fusion protein that acts as a ligand trap to competitively bind and neutralize TGF- β ligands, is an exciting therapeutic prospect that attenuates PAH through reversing pulmonary artery remodeling, improving RV geometry, and restoring RV function in one pre-clinical model [118–120]. In the recently completed PULSAR trial, 106 patients with PAH on baseline therapies were treated with sotatercept or placebo (<https://clinicaltrials.gov/ct2/show/NCT03496207>). Preliminary results indicate that after 6 weeks, there were improvements in right heart strain, exercise capacity, and a statistically significant reduction in PVR compared to placebo. The SPECTRA study is underway to examine the effects of sotatercept in adults with PAH and WHO-FC III symptoms (<https://clinicaltrials.gov/ct2/show/NCT03738150>).

Modification of abnormal growth factor signaling in PAH is an area of active interest; tyrosine kinase inhibitors have shown mixed results in the treatment of PAH [103]. Imatinib demonstrated an improvement in exercise capacity and hemodynamics in the IMPRES trial but disappointingly had serious adverse events (subdural hemorrhage in patients receiving vitamin K antagonists) that prevented further use in the treatment of PAH [121, 122]. GB002 is an inhaled nonselective inhibitor of platelet-derived growth factor receptor- α and - β that showed a reduced right ventricular systolic pressure and mean PAP, as well as reduced pulmonary arteriolar muscularization, restoration of BMPR2 signaling, and

reduced NT-proBNP and cytokine levels in GB002-treated animals [123]. A phase 1 trial to investigate safety, pharmacokinetics, and pharmacodynamics of GB002 in patients with PAH is currently underway (<https://clinicaltrials.gov/ct2/show/NCT03926793>). Given the wide range of possibilities for developing novel therapies that modulate underlying pathobiological mechanisms underpinning this disease, future researchers must collaborate to prioritize pre-clinical and clinical studies of new therapeutics.

The Unmet Need of Group 2 and Group 3 PH

More than 75% of all cases of PH are attributed to left heart disease or chronic lung diseases [124, 125]. Despite the fact that PAH only accounts for 3% of all cases of PH, significant efforts to understand the pathologic mechanisms underpinning PAH have been undertaken, which have led to the development of investigational novel therapies targeting implicated pathogenic pathways [103]. There is much need for a similar approach to PH in left heart disease and chronic lung disease-associated PH.

Pulmonary hypertension in left heart disease and chronic lung disease-associated pulmonary hypertension encompass heterogeneous groups of multiple diseases that portend a poor prognosis [126, 127]. Pulmonary hypertension in left heart disease includes HFrEF, HFpEF, valvular heart disease, and heart disease resulting from chronic arrhythmias [128]. The traditional thinking is that PH in left heart disease results from passive pulmonary vascular congestion related to increased left-sided filling pressures (defined hemodynamically as isolated post-capillary PH with mean PAP > 20 mmHg, pulmonary arterial wedge pressure (PAWP) > 15 mmHg, and a PVR < 3 WU). However, in some instances, the elevated left-sided pressures do not completely account for remodeling that may develop over time and thus lead to combined pre- and post-capillary PH (defined hemodynamically as mean PAP > 20 mmHg, PAWP > 15 mmHg, and a PVR \geq 3 WU that resembles the “pulmonary vascular phenotype” of PAH (with mean PAP > 20 mmHg, PAWP \leq 15 mmHg, and a PVR \geq 3 WU) [128]. Chronic lung disease-associated PH occurs most commonly in COPD and interstitial lung diseases and although is defined by the same hemodynamic properties as PAH (pre-capillary PH or a “pulmonary vascular phenotype”), it represents independent complex and multifactorial pathologic processes [129]. It is not surprising then that defining these groups solely based on strict hemodynamic definitions is problematic. To date, most studies using currently available advanced therapies (i.e., pulmonary vasodilators) in PH in left heart disease have focused on patients with HFrEF and isolated post-capillary PH; all such studies have been negative, or proved to be harmful [126, 128]. Studies of pulmonary vasodilators in chronic lung disease-associated PH have been limited to patients with COPD or idiopathic pulmonary fibrosis, only one of the many subtypes of fibrosing lung

diseases. While mostly disappointing, recent studies using inhaled NO [130] and inhaled treprostinil showed promising results in patients with idiopathic pulmonary fibrosis and any form of interstitial lung disease, respectively (<https://clinicaltrials.gov/ct2/show/NCT02630316>).

If we are to advance our understanding of the pathophysiology of and treatment options for PH in left heart disease and chronic lung disease-associated PH, we need to focus attention on defining clinical and hemodynamic sub-phenotypes, discovering disease-specific biomarkers, establishing scoring and risk stratification systems, and developing carefully controlled trials that do not exclude disease subtypes (such as HFpEF, left heart disease with combined pre- and post-capillary PH, undefined subtypes of idiopathic interstitial pneumonias, or other chronic lung diseases) [126, 129]. Improved understanding and effective treatments of WHO Groups 2 and 3 PH must include a multimodality approach that combines currently available disease-specific standard of care therapies with novel therapies targeting the underlying pathology that leads to PH.

Summary

The management of PAH is increasingly complex. Specialized centers are best suited to provide the comprehensive care management required. With the growing number of therapeutics clinically available, intimate knowledge of pharmacology and side effects is integral to providing optimal care for this vulnerable and high-risk patient population. In addition, patients with PAH often present with multiple comorbidities further complicating management or even call to question the type of PH. Interventional strategies remain largely palliative in nature or serve as a bridge to transplantation.

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Compliance with Ethical Standards

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